REVIEW ARTICLE

Food protein-induced enterocolitis syndrome: Pitfalls in the diagnosis

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Abstract

Food protein-induced enterocolitis syndrome (FPIES) represents the severe end of the spectrum of gastrointestinal food hypersensitivity; its acute episodes can culminate in severe dehydration and hypovolemic shock, and its chronic form entails considerable morbidity associated with feeding difficulty and failure to thrive. Nevertheless, awareness for this syndrome remains rather low. Many factors hamper the establishment of FPIES diagnosis. Such factors pertain to the pathophysiological mechanism of the syndrome, causal food proteins, clinical manifestations, diagnostic procedures, differential diagnosis considerations, and prevailing perceptions which may require critical appraisal. Throughout this review, we will present and discuss these issues and put the focus on factors that could lead to under-diagnosis of FPIES, cause numerous acute episodes, and substantially increase the diseases morbidity and financial burden. We will also address other issues that are clinically relevant to FPIES.

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food hypersensitivity syndrome which manifests with severe symptoms from the gastrointestinal tract. It rarely appears after the first year of life, with a mean age of initial presentation of 5.5 months (1–3). The first report of FPIES dates back to 1940 (4). More insight was provided by Gryboski (5) and Powell (6–8) who described the basic characteristics of the syndrome in infants presenting with severe diarrhea and vomiting induced by cow's milk (CM).

Although historically perceived as a rare syndrome, a rather considerable prevalence of 0.34% has recently been reported in a large-scale, prospective, population-based study (9). This raises the question of whether under-diagnosis of FPIES has thus far caused underestimation of its prevalence. Indeed, differential diagnosis of FPIES is challenging, as it is hampered by many of the diseases pathophysiological features. Furthermore, the morbidity of the chronic form is associated with feeding difficulty and failure to thrive, and the acute episodes may lead to severe dehydration and hypovolamic shock; these further underscore the importance of a prompt diagnosis. We therefore opted to review FPIES from this perspective and emphasize the factors that could impede differential diagnosis and hamper identification of patients. Alongside such issues, we present and discuss additional information of clinical relevance pertaining to basic aspects of FPIES.

Diagnostic considerations

- Food protein-induced enterocolitis syndrome is perceived as a rare syndrome, and therefore, it is not included in the initial diagnostic approach of the clinician. Nevertheless, it probably is more prevalent than previously appreciated.

Which foods usually cause FPIES?

Cow's milk and soy have been implicated as eliciting factors from the very first reports of FPIES and are the usual offending foods (1, 10, 11). Nevertheless, solid foods (rice (12), chicken, egg, nuts oat, barley, green peas, sweet potatoes, lentils, fish, shellfish, egg (13), fruits (14), etc.) have also been demonstrated to cause a frequently more severe form of the syndrome. In that respect, rice-induced FPIES is suggested to be fairly common and particularly severe (2, 11, 12, 15, 16). In fact, solid-food FPIES is affecting infants of a higher mean age than the CM-/soy-induced equivalent, probably mirroring the normal temporal succession of food introduction in their diet. Solid-food FPIES has also been reported in adult age following ingestion of seafood (17), albeit such a late onset is rare. Thus, diversity in time of onset questions the usefulness of generalized guidelines regarding the timeline of FPIES appearance. The ease of diagnosing solid-food FPIES is also affected by breastfeeding: Exclusively, breastfed infants are not exposed to

CM/soy, and therefore, there are no signs of potential food hypersensitivity until the time of solid food feeding (and the subsequent acute solid-food FPIES episodes). Conversely, infants that are not exclusively breastfed are exposed to CM/soy, and therefore, an early reaction to CM/soy may indicate a potential propensity to future solid-food FPIES; indeed, FPIES episodes to CM/soy and solid food are strongly correlated. In any event, FPIES could probably be elicited by any food, suggesting that a high index of suspicion is required from the clinician. From this perspective, it is intriguing that egg, a food of considerable allergenicity, is rarely a cause of FPIES. This can probably be ascribed to its delayed introduction in the infants diet and subsequent avoidance of the 'window of physiologic susceptibility' (3). Conversely, food proteins traditionally believed to be of low allergenic potential are administered quite early in the course of weaning. They are therefore fairly often the unexpected cause of acute FPIES. Such paradoxical behavior further perplexes the syndromes diagnosis and implies that generalizations about food allergenicity may be inappropriate during evaluation of a potential FPIES patient.

Diagnostic considerations

- The perception that foods such as poultry, grains and vegetables are of negligible allergenic potential impedes their association with the patients symptoms. However, FPIES is frequently elicited by foods widely perceived as 'non-allergenic'.
- The existence of two discrete food subgroups with the potential to cause FPIES, that is, *CM/soy* and *solid foods*, further perplexes diagnosis. Clinicians should be aware of differences in severity and age of onset between these two trigger-defined disease types.

Diversity of clinical manifestations

The clinical features of FPIES vary considerably (13, 18). Both their nature and severity are directly depended on the age of the infant and the frequency of the food intake. Clinical manifestations of typical *chronic* FPIES usually begin in early infancy, often within 1–4 wk after introduction of CM (3). Regular administration of the offending food leads to chronic symptoms which include intermittent vomiting, diarrhea, irritability and failure to thrive. All symptoms are rapidly resolved following exclusion of the food from the infants diet (11) (Table 1). Nevertheless, its re-introduction following a period of avoidance will culminate in a full-blown *acute* FPIES episode. This entails severe clinical symptoms such as repetitive projectile vomiting with a typical elicitation timeframe of 1–3 h following food intake, lethargy, pallor, cyanosis, hypothermia, and diarrhea (2–10 h following food intake). The two later symptoms predispose for a markedly severe reaction (2) (Table 1).

Even though the clinical manifestations during an acute FPIES episode are rather typical, great variability in their nature, severity and timeframe of onset is common. In a retrospective case study of 35 patients, the most common

Table 1 Comparison of clinical manifestations and laboratory findings between chronic and acute FPIES

Clinical manifestations/laboratory findings during regular administration of causal food protein (chronic FPIES)	Clinical manifestations/laboratory findings following first-time introduction of causal food protein or re-introduction following an extended period of avoidance (acute FPIES)
Periodic vomiting Chronic	Profuse repetitive projectile vomiting Typically commencing 1–3 h following food intake (2)
Periodic diarrhea Chronic Potential presence of blood, leucocytes, eosinophils, reducing substances (13) and Charcot–Leyden crystals (25) in stool	Diarrhea (24%) (2) Typically commencing 2–10 h following food intake. Median 5 h Potential presence of blood, mucous, leucocytes eosinophils (32), increased levels of TNF-alpha (7, 26, 39), and carbohydrates (15) in stool
Lethargy/septic appearance (22)	Lethargy (21)/pallor (1)
Failure to thrive	Hypothermia < 36°C (24%) (2) Hypotension (15%) (15)
Dehydration	Dehydration Hypovolemic shock (20%) (2) Acidemia (15%)(22)
Abdominal distension (3)	Thrombocytosis > 500 × 10^9/l (63%) (2)
Methemoglobinemia (22)	Methemoglobinemia (35%) (21) Cyanosis
Lactose malabsorption (1) Anemia (1) Hypoalbuminemia (1)	Leucocytosis (15) (increase in absolute neutrophil count > 3500 cell/μl, absolute value 5500–16,800 cell/μl, median value 9900 cell/μl, maximum value 6 h following food intake) (15, 20) [reported in 90–100% of the patients (1, 7, 20)]

FPIES, food protein-induced enterocolitis syndrome.

clinical features were vomiting (100%), lethargy (85%), pallor (67%), and diarrhea (24%) (2); in another large retrospective study of 462 cases, vomiting was present in all patients and diarrhea was seen in 54% (19). However, others have reported no vomiting in up to 28% of confirmed FPIES patients (7). Accordingly, Hwang et al. (20) reported that two key symptoms of acute FPIES, vomiting and lethargy, were concomitantly observed in only 62% of patients after a positive oral food challenge (OFC); however, lethargy is a rather subjective symptom as compared to vomiting and diarrhea and, therefore, its assertion may be more confounded. The time of onset of diarrhea was also found to vary significantly (1).

Diagnostic considerations

- The clinical picture of the patient with FPIES varies depending on the frequency of the intake of the inciting food. This further obscures a link of such diverse symptoms with a single underlying disease. It should therefore be realized that FPIES can present in two forms, that is, *acute* and *chronic*, with marked differences in the severity of symptoms.

Usefulness of laboratory findings

Food-specific IgE antibody levels are typically undetectable, and skin prick tests (SPTs) with the causative food are negative in up to 90% of patients with FPIES (20, 21). Nevertheless, positive results have been reported and correlate with a prolonged course of the syndrome and decreased probability of tolerance induction (11, 22, 23). Therefore, SPTs have some use in *monitoring* of established disease (as opposed to its *diagnosis*) (15). This is further supported by a suggested link of FPIES to atopy (22) and the existence of an atypical IgE-positive FPIES phenotype (13). Furthermore, SPTs can be used to rule out *current* IgE reactivity, as some patients may go on to develop IgE-dependent food allergy in the future. In any event, the use of SPTs is not indicated for the diagnosis of FPIES. In regard to atopy patch tests (APTs), one study reported negative and positive predictive value as high as 100% and 75%, respectively (10). However, these promising findings have been challenged by two recent studies, one of which investigated a total of 462 patients (19, 24); this scarcity of reports and the marked phenotypic differences between cutaneous and gastrointestinal T lymphocytes (13) do not allow for firm conclusions regarding the diagnostic usefulness of APTs (15, 20, 22).

Methemoglobinemia is reported during severe acute FPIES (21, 22) and is ascribed to reduced action of catalase due to overproduction of intestinal nitrates (15). Although this finding appears to be FPIES specific, its sensitivity is low (25), hence lowering its usefulness as a diagnostic tool. Accordingly, the findings of endoscopy and/or intestinal biopsy are variable and non-specific. They often include diffuse inflammation consisting of lymphocytes, plasmacytes, eosinophils and mast cells (15, 26) with or without illeal involvement (1, 22), friable and/or hemorrhagic intestinal mucosa with ulcers (15, 22, 27), as well as edema and villous atrophy (22).

Gastric juice leukocytosis is an intriguing diagnostic option, and it could constitute a future criterion of food challenge positivity (20). However, it is currently a research tool rather than a validated diagnostic test, and further investigation is warranted before it can be routinely utilized in clinical practice.

Thrombocytosis (>500 $\times$ 10^9 cells/l) following intake of the offending food was reported in 63% of a patient cohort (2), possibly due to platelet release from the spleen caused by epinephrine overproduction. Nevertheless, this test's low sensitivity and specificity limit its usefulness. Accordingly, C-reactive protein tests are also unsuitable as shown from conflicting evidence (20, 28).

In contrast to the aforementioned laboratory findings which are generally inconclusive, leucocytosis is a prominent component of acute FPIES. An absolute neutrophil count rise of >3500 cells/l over the baseline is reported in over 90% of patients after ingestion of the culprit food (1, 7, 18). However, although this tests sensitivity is high, its specificity is limited, as leucocytosis is a feature of numerous pathologic conditions including infectious diseases, a key consideration in FPIES differential diagnosis. Metabolic acidosis and an abnormal stool smear test, although correlated with FPIES, are also findings typical of sepsis-like illnesses and fall short in effectively supporting diagnosis of FPIES.

Diagnostic considerations

- To date, there is a lack of pathognomonic and definitive diagnostic tests for FPIES. The only validated *in vivo*/*in vitro* test that is reliably sensitive, that is, leucocytosis, suffers from limited specificity and cannot effectively pinpoint FPIES. Therefore, its diagnosis is currently depended on clinical criteria.

Reaching a diagnosis

Identifying FPIES patients is a challenging undertaking as exemplified by the extreme report of a patient who underwent five intensive care unit admissions before diagnosis was set (11). Furthermore, a correct diagnosis was established in only 11% of patients presenting with an acute episode, whereas the rest received no diagnosis or a diagnosis of viral infection, sepsis, intussusception and/or 'food allergy' in general (2). Accordingly, 34% of another patient cohort underwent gastric X-ray and up to 8% underwent electrocardiogram, electroencephalogram and even investigational laparotomies (2, 29, 30).

Insofar as diagnosis is set on a clinical basis, a thorough medical history is invaluable (19, 31). Failure to gain weight (<10 g/day) is correlated with *chronic* FPIES (32). Accordingly, factors strongly indicative of *acute* FPIES are prior sudden-onset episode(s) following intake of the suspect food, exclusion of other potential FPIES-mimicking diseases, and symptom resolution after food omission from the patients diet (15, 25, 33). It should also be noted that previous uneventful ingestion of the suspect food does not rule out acute FPIES, as the reaction can occur after repeated feedings. Indeed, only 61% of a patient cohort reacted upon first-time-ingestion of the offending food, whilst the rest tolerated it for up to three administrations before experiencing an acute episode (2).

When the medical history is strongly supportive of FPIES, an OFC is not required to set the diagnosis (22). Nevertheless, when history is inconclusive, reappearance of the symptoms following an OFC is indicative of the syndrome. OFCs are also important for the follow-up of established disease, as they are the main tool for confirming tolerance induction (22). Challenging a patient with established or suspected FPIES is a high-risk procedure and should be carried out in a hospital setting under close supervision and with an IV line in place (15) (Fig. 1).

Diagnostic considerations

- In acute FPIES, the severity of the patient's condition could initially divert the clinician from diagnosing the syndrome. However, taking a detailed medical history is imperative as it will provide valuable information about prior reactions and/or newly introduced foods.
- Report of previous uneventful ingestion of the suspect food should not rule out FPIES; reacting upon later feedings is not uncommon.

Why is it so hard to identify?

A plethora of pathologic entities present with symptoms mimicking an acute FPIES episode. These include – but are not restricted to – infectious diseases (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia* sp., etc.), metabolic and coagulation disorders (34), gastroesophageal reflux disease, gastrointestinal bleeding, and endocrine diseases (35). It is also important to rule out surgical abdominal emergencies presenting with FPIES-like symptoms, in order to avoid non-required surgical procedures. Necrotizing enterocolitis, intussusception, and Hirshprung disease are the three most common conditions leading to misdiagnoses in a surgical context. In fact, in FPIES patients, detection of intramural gas on abdominal radio-

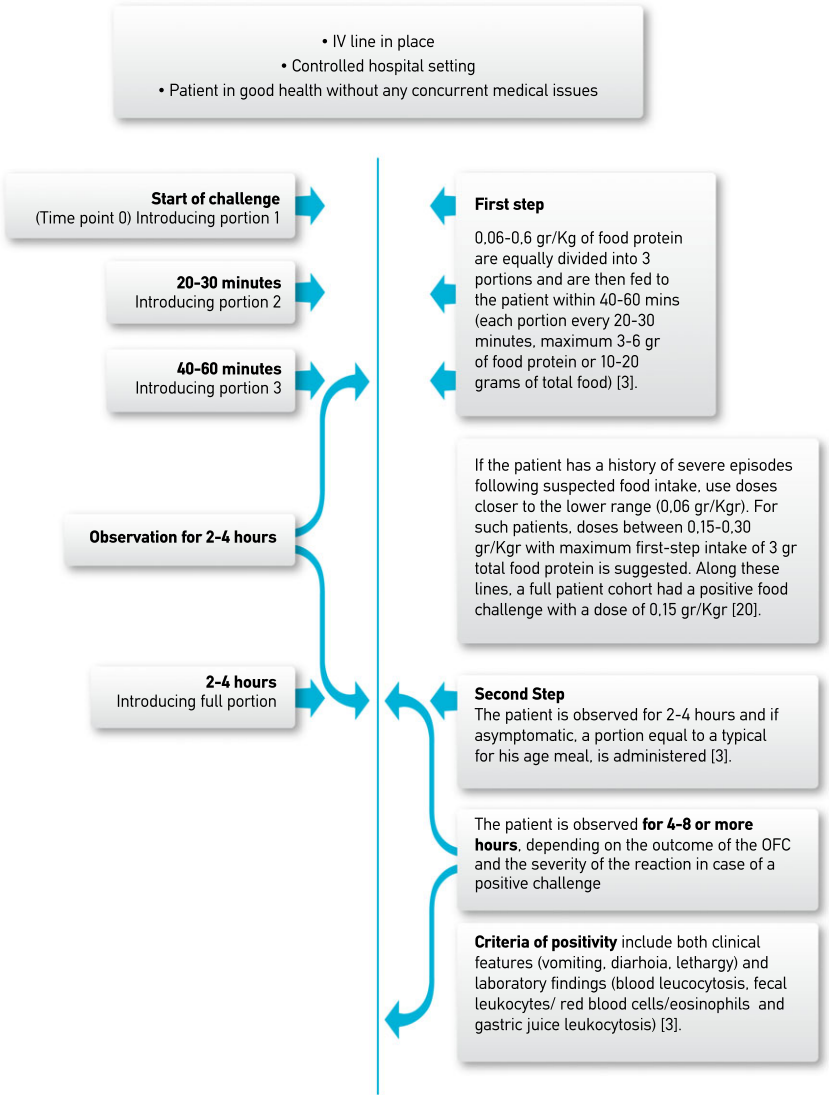

Figure 1 Oral food challenge (OFC) procedure. Different centers may use altered protocols regarding the timing and number of food administrations, as well as regarding the time period of patient observation. A recent report also suggests that oral rehydration may be sufficient for mild reactions (9); however, such a protocol may not be appropriate for all populations (and especially for infants with severe reactions) and has to be validated by further research. Strict safety measures should be instituted, and an IV line should be in place at the beginning of the OFC.

Table 2 Features of the gastrointestinal disorders of allergic origin that are implicated in differential diagnosis with FPIES, as compared with the respective features of FPIES

	Disease-specific features	Shared features	Disease-specific features	
Proctocolitis	No vomiting Normal or loose stools (34) Diarrhea rare (15) Good general condition Onset usually within the first 3 months Mostly within the first 6 months (34) Usually breastfeeding (60%) (25) Normal growth (22) Tolerance induction usually by 1 yr of age (34) Normal hematocrit (37) Anemia rare (25, 34) No severe symptoms following food reintroduction after a period of avoidance Blood eosinophilia possible (15) No leucocytosis (35)	Bloody stools No detection of food-specific IgE Negative skin prick tests (SPTs) (34) Avoidance of causal protein leads to symptom resolution (34)	Vomiting prominent (22) Diarrhea prominent Affected general condition Onset usually within the first 3–6 months, possibly up to 1 yr Cases of onset at an older age reported (1, 3) Breastfeeding very rare Usually on cow Milk/soy formula or during weaning Failure to thrive (22) Tolerance induction usually by 3 yr of age, albeit it is food and other factors depended and can last for a lot longer (3, 15) Anemia possible (1) Acute episode with severe symptoms following food reintroduction after a period of avoidance No blood eosinophilia (15) Leukocytosis in >90% of patients (1, 20)	**FPIES**
Enteropathies	No bloody stools Vomiting intermittent (22) No severe symptoms following food reintroduction after a period of avoidance No acidemia (35) No methemoglobulinemia (35)	Diarrhea Vomiting Hypoalbuminemia Anemia (34) Failure to thrive (34) No detection of food-specific IgE Negative SPTs (34) Avoidance of causal protein leads to symptom resolution (34)	Bloody stools Vomiting prominent (22) Acute episode with severe symptoms following food reintroduction after a period of avoidance Acidemia possible (15%) Methemoglobulinemia possible (35%) (21)	
Eosinophilic disorders	Blood eosinophilia ranging from 50% (EE) to 66% (EG) (25) (up to 75% reported) (37) Detection of food-specific IgE-Positive SPTs (34) (in approximately 50%) (15) Onset at any age (25) Can last into adulthood (25) Usually caused by multiple food proteins (22)	Diarrhea (EG) Vomiting Hypoalbuminemia Anemia Failure to thrive (37) Atopic predisposition in 70–80% of patients (15, 25) Avoidance of causal protein leads to symptom resolution	No blood eosinophilia (15) No detection of food-specific IgE Negative SPTs (34) Onset usually within the first 3–6 months, possibly up to 1 yr. Cases of onset at an older age reported (1, 3) Tolerance induction usually by 3 yr of age, albeit food dependency exists and can last for much longer (15) Food protein specific	

EE, eosinophilic esophagitis; EG, eosinophilic gastritis; FPIES, Food protein-induced enterocolitis syndrome.

graphs could erroneously prompt a diagnosis of necrotizing enterocolitis (3). Nevertheless, symptoms of acute FPIES are bound to subside within a few hours of fluid resuscitation; this is not the case for sepsis and/or surgical emergencies, and this will assist in differential diagnosis from these conditions.

Diseases of allergic background such as IgE-mediated reactions, non-IgE-mediated reactions (allergic proctocolitis and food protein-induced enteropathy) (36), and mixed IgE-/non-IgE-mediated reactions (eosinophilic esophagitis, gastritis, and colitis) (37) also need to be distinguished from FPIES. Regarding immediate (IgE-mediated) reactions, potential cutaneous and respiratory symptoms and the typical time frame of onset (i.e., <1 h following food intake) are important diagnostic clues (3). In regard to the rest of the food-induced allergic disorders, a detailed presentation of clinical and laboratory findings and their comparison with FPIES features are presented in Table 2.

It is thus apparent that a high index of suspicion is required upon presentation of a patient with clinical manifestations resembling FPIES. Even the well-documented protection provided by breastfeeding has recently been challenged (28, 38). To date, this protection has been an important diagnostic clue which has allowed exclusion of an FPIES diagnosis in exclusively breastfeeding infants. Therefore, consultation with a pediatric subspecialist (allergist/immunologist/gastroenterologist) is important in an attempt to establish the diagnosis, identify the culprit food, and design an appropriate management plan.

Diagnostic considerations

- In an acute episode, the patient often presents with severe septic-like clinical manifestations resembling infection, metabolic disorders, or surgical emergencies. However, rapid and complete symptom resolution following fluid resuscitation is a characteristic of acute FPIES and is typically not seen in these conditions.

Knowledge on pathophysiology still lacking

As the diagnosis of FPIES is set clinically, information pertaining to the syndromes pathophysiology is limited and warrants

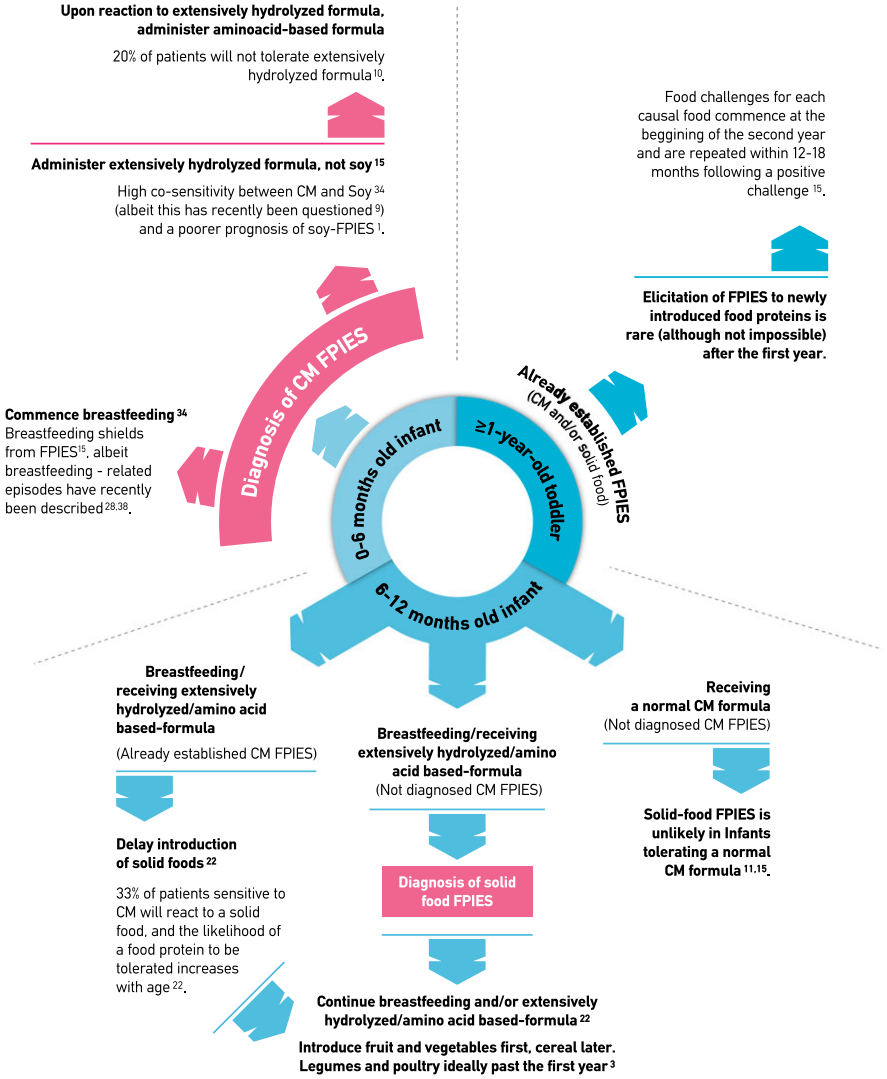

Figure 2 Treatment algorithm. The schematic assumes that administration of solid foods will commence upon the 6th month. If solids are introduced earlier (e.g., the 4th month), then the guidelines in regard to the 6th–12th months are extended (e.g., 4th–12th month). This algorithm is based on current knowledge and is likely to change as new data become available (e.g., recent evidence questions the protective effect of breastfeeding and/or the high cross-reactivity between cow's milk [CM] and soy).

further characterization (13). Current paradigm maintains that FPIES is underpinned by mucosal inflammation and increased intestinal permeability. To date, there is substantial evidence to suggest the involvement of antigen-specific T cells and eosinophils as well as cytokines such as TNF-alpha, IL-10, and TGF-beta (13). Indeed, TNF-alpha may play a role in the pathophysiological mechanism of FPIES, as its expression is elevated in the intestinal epithelial cells and CM-specific T cells of patients (26, 39). Impaired production of the epithelium-protecting cytokine TGF-beta could also be important for FPIES pathophysiology. IFN-gamma and IL-4 are also implicated (1, 9), albeit the exact underlying mechanism is unclear (1, 11).

Diagnostic considerations

- The pathophysiological mechanisms underpinning FPIES must be dissected and dealinated in order for the clinician to achieve a solidly structured diagnostic approach.

Immediate treatment and long-term follow-up

The mainstay of the treatment of acute FPIES is rigorous intravenous (IV) resuscitation to avoid a hypovolemic shock. This will likely be sufficient for the patient's successful recovery (3). The use of corticosteroids, although under debate, could assist in arresting the inflammatory cascade (22). Conversely, epinephrine will offer no significant assistance as the hypovolemic condition is not angiogenic but is caused by substantial GI liquid loss. Ondansetron hydrochloride, a drug widely used to prevent vomiting induced by chemotherapy and radiation, has been recently suggested to be of value for the management of acute FPIES (40); however, further research is warranted. Apart from the management of the acute episode, FPIES treatment entails long-term follow-up of the patient and an organized effort to reintroduce the incriminated foods in his/her diet. Treatment should be individualized as it is influenced by a plethora of factors. These include the patients age, the number and nutritional value of the inciting food(s), the severity of the acute episodes as well as specific IgE titers and potential atopic predisposition; all these also dictate the time schedule of the food challenges (22). Regardless of individualization, the basis of every patients follow-up consists of certain well-documented and simple guidelines: (i) Identification of causal food and its complete omission from the patients diet (22), (ii) uninterrupted administration of every other food that the patient tolerates, (iii) titrated food challenges under supervision, undertaken on a case-by-case basis to identify potential tolerance induction, and (iv) re-introduction of the incriminated food upon establishment of tolerance.

Extending elaborate follow-up guidelines for already established disease is beyond the scope of this review. Nevertheless, a brief algorithm outlining treatment measures is presented in Fig. 2.

Concluding remarks

Considering that the differential diagnosis of FPIES is a challenging task, the syndrome is likely under-diagnosed. However, the potential of FPIES to cause near-fatal episodes if not identified early underscores the necessity for a high index of suspicion for this condition. Timely diagnosis will contribute to the reduction of its substantial morbidity and of the financial burden associated with the patients multiple hospital admissions.

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